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Review

Gluten-free and casein-free diets in the treatment of autism spectrum disorders: A systematic review

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ABSTRACT

This paper systematically reviews research on the effects of gluten-free and/or casein-free (GFCF) diets in the treatment of ASD. Database, hand, and ancestry searches identified 15 articles for review. Each study was analyzed and summarized in terms of (a) participants, (b) specifics of the intervention, (c) dependent variables, (d) results, and (e) certainty of evidence. Critical analysis of each study's methodological rigor and results reveal that the current corpus of research does not support the use of GFCF diets in the treatment of ASD. Given the lack of empirical support, and the adverse consequences often associated with GFCF diets (e.g., stigmatization, diversion of treatment resources, reduced bone cortical thickness), such diets should only be implemented in the event a child with ASD experiences acute behavioral changes, seemingly associated with changes in diet, and/or medical professionals confirm through testing the child has allergies or food intolerances to gluten and/or casein.

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1. Introduction

The term autism spectrum disorder (ASD) refers to a range of neurodevelopmental disorders that include the more specific diagnoses of autism, Asperger syndrome, and pervasive developmental disorder not otherwise specified (Sturmey & Fitzer, 2007). The defining features of ASD include impairments in social interaction, communication, imagination, restricted interests, and stereotypic behaviors. These symptoms range in severity from mild to debilitating and usually persist throughout the lifespan (National Research Council, 2001). In addition to the symptoms used in diagnosis, several serious co-morbid conditions are also commonly associated with ASD including intellectual disability, depression, and epilepsy (Filipek et al., 1999). Current estimates suggest that the prevalence of ASD is approximately 6.7 cases per 1000 children or approximately 1 in every 150 children (Centers for Disease Control and Prevention, 2007).

While the etiology of ASD remains unknown, emerging evidence suggests multiple gene defects may be involved in tandem with an environmental catalyst (Cusco et al., 2009). The ongoing confusion regarding the etiology of ASD has lead to the consideration of many possible causes. Often these potential causes are translated into treatments and then propagated to the public before sufficient evidence regarding effectiveness or safety exists (Heflin & Simpson, 1998; Metz, Mulick, & Butter, 2005). One persistent etiological theory implicated insufficient enzymatic activity, increased gastrointestinal permeability, and the absorption of toxic byproducts of incompletely digested proteins from dairy (casein) and cereals (gluten). This theory is often called the "the Opioid-Excess Theory" (Panksepp, 1979; Reichelt et al., 1981; Reichelt, Knivsberg, Lind, & Nodland, 1991; Reichelt, Knivsberg, Nodland, & Lind, 1994; Shattock, Kennedy, Rowell, & Berney, 1990; Wakefield et al., 1998; Whiteley, Rodgers, Savery, & Shattock, 1999).

In typical functioning gastrointestinal tracts, enzymatic activity breaks proteins into peptides, and transforms peptides into amino acids. The intestinal lining then absorbs the amino acids into the blood stream, which carries the amino acids to the rest of the body, providing nutrition. The Opioid-Excess Theory alleges ASD can result from disruptions to this process. According to the theory, some individuals suffer from inadequate production of gluten- and casein-related digestive enzymes, and increased gut permeability. Without adequate levels of digestive enzymes, peptides derived from gluten and casein fail to become amino acids in large numbers. Increased gut permeability then allows the peptides to leak into the blood stream, where they circulate and eventually cross the brain–blood barrier. Symptoms of ASD are theorized to result from peptides' attaching to opioid neuro-receptors.

Different researchers investigating aspects of this theory often obtain conflicting results. Horvath, Papadimitriou, Rabsztyn, Drachenberg, and Tildon (1999), for example, examined the upper gastrointestinal tracts of 36 children with ASD who were experiencing chronic gut related symptoms (e.g., diarrhea, constipation, and/or bloating) and found that 85% of the children suffered from at least one gastrointestinal problem compared to 12% of a control group of children without ASD. Black, Kaye, and Jick (2002), in contrast, found no evidence that children with ASD were more likely than children without to have had gastrointestinal disorders at any time before their diagnosis. As Metz et al. (2005) noted, the potential relation between gastrointestinal problems and ASD, even if prevalence is significantly higher in ASD groups than in control groups, is still a correlation at best.

Another variable that has been implicated in ASD is urinary peptide levels (UPLs). Specifically, if children with ASD are not turning peptides into amino acids, then more peptides should be present in the urine of children with ASD than in children without ASD. While some researchers have indeed detected increased UPL in samples of children with ASD (Reichelt et al., 1991), others have found no significant differences (Alcorn et al., 2004; Cass et al., 2008; le Couteur, Trygstad, Evered, Gillberg, & Rutter, 1988; Williams, Shattock, & Berney, 1991). Further complicating the issue, Alcorn et al. (2004) suggested "there may be regional differences in the urinary profile. . .the characteristics of a population in England, both with and without autism [may be], different from those of in [*sic*] Scandivania" (p. 278). Due to the potential variance in regional UPLs, detecting abnormal UPLs may be more complex than has been considered in previous research.

Research on gut permeability in children with ASD is similarly characterized by conflicting data. D'Eufemia et al. (1996) and Horvath and Perman (2002) found abnormally high levels of intestinal wall permeability in 43% (9/21), and 76% (19/26) of study participants, respectively. In contrast, Robertson et al. (2008) report finding levels of intestinal permeability that were statistically equivalent across groups of children with and without ASD. Comparably, Kemperman, Muskiet, Boutier, Kema, and Muskiet (2008) found 23 children with pervasive developmental disorder (PDD) all had levels of intestinal permeability within the accepted normal range (van Elburg et al., 1995). Overall, regarding the Opioid-Excess Theory's premise that elevated UPLs lead to heightened gut permeability, no correlational evidence exists for a relation between UPLs and degree of gut permeability (Filipek et al., 1999).

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There is evidence showing that peptides formed from casein and gluten can cross the blood–brain barrier (Lindström, 1984; Sun & Cade, 1999, 2003; Sun, Cade, Fregly, & Privette, 1999). However, causal relations involving the peptides' attachment to opioid neuro-receptors have been demonstrated only in animal models (Sun et al., 1999; Sun & Cade, 1999, 2003). Sun et al. (1999) and Sun and Cade (2003) found peptides from casein and gluten activate a variety of regions of rats' brains. The researchers observed abnormal behaviors only in response to administration of peptides derived from casein. Although this has been interpreted as evidence that such a mechanism can cause autism, the central role of human language and social deficiencies in defining ASD currently prevents the interpretation of unusual rat behavior as equivalent to human autistic behavior.

Despite the need for continued research regarding the mechanism of action for the Opioid-Excess Theory, interventions based on this theory have already arisen. Some of the research regarding these interventions suggests it may be possible to ameliorate, or even eliminate, autistic symptoms by not allowing the individual with an ASD to ingest gluten or casein (for a claim of "normalizing" autism see Knivsberg, Reichelt, & Nodland, 1999). The gluten-free and casein-free (GFCF) diet intervention appears to be widely used. Green et al. (2006), for example, surveyed 552 parents of children with ASD and found that alternative diets had been implemented with 9.9% of children with Aspergers syndrome, 29.4% of children with mild autism, and 32.2% of children with severe autism.

When selecting interventions and treatments for ASD, many parents feel it is better to "leave no stone unturned" and implement any available treatment that seems to do no harm, especially if the treatment is easy to implement, requires little time, and is widely accepted (Elder, 2008; Green, 2007; Metz et al., 2005). However, the common assumption that the GFCF diet has no negative side effects may not be accurate. In addition to the possible divergence of treatment resources (e.g., money to buy special foods, time required to prepare separate meals), specialized diets have the potential to be socially stigmatizing. For example, the child with ASD may not be able to eat the same foods as peers at a party or in the local restaurant.

The GFCF diet has also been linked to health risks. One concern is the increased risk of nutritional deficiencies. Arnold, Hyman, Mooney, and Kirby (2003), for example, collected plasma amino acid profiles of 36 children with ASD and found them more likely to have nutritional deficiencies and lower plasma levels in essential amino acids. Children on the GFCF diet were significantly more at risk than the rest of the children with ASD in this study. This difference may be due to the lack of proteins specifically found in gluten and casein and/or the increase in food refusal which may follow the implementation of a GFCF diet (e.g., Irvin, 2006). Hediger et al. (2008) found that in a group of 75 boys between 4 and 8 years of age, on casein-free diets showed signs of suboptimal bone development, specifically reduced bone cortical thickness. Although this study did not assess children's intake of calcium and vitamin D (two nutrients bones require to develop optimally), Hediger et al.'s findings do serve as a warning for what could result from dairy abstinence in some children with ASD.

Given that large numbers of children with ASD may be on GFCF diets, the widely propagated claims that such diets can ameliorate the symptoms of ASD, and the potential social and health risks associated with the GFCF diet warrant a careful review. At least three recent papers have been published that provide overviews of portions of this research (Christison & Ivany, 2006; Elder, 2008; Page, 2000). These reviews are informative, but did not provide a comprehensive, systematic review of all available GFCF intervention research. To facilitate evidence-based practice in this important area, we herein provide a systematic review of all available studies in which a GFCF diet was used to treat ASD. The objective of this review is to describe the characteristics of these studies (e.g., participants, intervention procedures), evaluate intervention outcomes, and appraise the certainty of the evidence for the existing corpus of intervention studies. A review of this type is primarily intended to guide and inform practitioners in the decision to implement GFCF diets.

2. Methods

This review involved a systematic analysis of studies that focused on the treatment of ASD with GFCF diets. Each identified study that met pre-determined inclusion criteria was analyzed and summarized in terms of (a) participants, (b) specifics of the intervention, (c) results, and (d) certainty of evidence. To assess the certainty of evidence we critically appraised each study's design and related methodological details (e.g., presence or absence of an experimental design). Given our aim to review all available studies, and the fact that the studies used various and inconsistent research methodologies (e.g., single-subject experimental designs, randomly controlled trials, non-experimental group designs, etc.), our review approach is dominantly narrative, and when possible, quantitative.

2.1. Search procedures

Systematic searches were conducted in four electronic databases: PsycINFO, Psychology and Behavioral Sciences Collection, Educational Resources Information Clearing House (ERIC), and MEDLINE. Publication year was not restricted, but the search was limited to English language peer-reviewed journals. On all four databases, the terms "diet", "autism", "autistic", "Asperger syndrome", "gluten", "casein", and "nutrition" were inserted as free text into the keywords field. The abstracts of the resulting 118 studies were reviewed to identify studies for inclusion (see Section 2.2). The reference lists for studies meeting these criteria were also reviewed to identify additional articles for possible inclusion. Hand searches, covering 2008–March 2009, were then completed for the journals that had published the included studies. A total of 134 articles were screened for possible inclusion.

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2.2. Inclusion and exclusion criteria

To be included in this review, the study had to meet three inclusion criteria. First, a study had to contain at least one person with an ASD, including autism, Asperger syndrome, or pervasive developmental disorder, not otherwise specified (PDD-NOS). Second, the intervention being investigated had to involve a diet that removed or reduced the consumption of gluten and/or casein. Finally, the dependent variable had to be in some way related to the amelioration of ASD symptoms, for example, improved communication, or emotional reciprocity. Studies were excluded if they (a) summarized intervention research, but did not conduct a diet manipulation (e.g., Elder, 2008), (b) if procedures were implemented without oversight or direction from researchers (e.g., parent description of intervention and results) (e.g., Akerley, 1976) and, (c) if the only measured outcomes were unrelated to autism symptoms (e.g., bone cortical thickness Hediger et al., 2008). Additionally, Knivsberg, Reichelt, Hoien, and Nodland (2003) was excluded after concluding both it and Knivsberg, Reichelt, Hoien, and Nodland (2002) were reporting results from the same study.

2.3. Data extraction

Each potential study was first assessed for inclusion independently by the first and second author of this review (see Section 2.4). Then each study was summarized in terms of the following features: (a) participants with an ASD whose diet was restricted, (b) the exact nature of the dietary restriction and any other intervention component (i.e., the independent variable), (c) the certainty of evidence, and (d) results of the intervention. Various procedural aspects were noted, including experimental design, inter-observer agreement, treatment integrity, follow-up data, and operational definitions of outcome measures. The ability of a study to provide certainty of evidence was rated as either "suggestive", "preponderant" or "conclusive" based on previous definitions (Schlosser, 2009; Simeonsson & Bailey, 1991; Smith, 1981).

The lowest level of certainty is classified as suggestive evidence. Studies within this category might have utilized A–B or intervention only designs, but did not involve a true experimental design (e.g., group design with random assignment and a control group, multiple-baseline or an ABAB single-subject design (Barlow, Nock, & Hersen, 2009)). The second level of certainty was classified as preponderance of evidence. Studies within this level had the ability to demonstrate that outcomes were likely due to the intervention. In this review, studies rated as providing a preponderance of evidence contained the following five qualities: (a) experimental designs, (b) when appropriate, adequate inter-observer agreement and treatment fidelity measures (i.e., 20% or more of sessions with 80% or better agreement), (c) operationally defined dependent variables, (d) enough detail to enable replication, and (e) limitation(s) regarding controls against alternative explanations for treatment outcomes (e.g., maturation, concurrent interventions, problems with construct validity). The final level of certainty was classified as conclusive. Within this level, studies not only possess the qualities of the preponderance level, but also attempt to control for alternative explanations of treatment gains (e.g., double-blind, placebo controlled, randomized control trial that controlled for the use of other interventions).

After it was determined what level of certainty a study's methodology was capable of providing, the results of that study were coded. Results were coded as "positive", "negative", or "mixed". Positive was reported if all participants in a within-subject design made improvements and if statistically significant differences were found in a group design (using the alpha levels stated in the reviewed study). Negative was reported if none of the participants in a within-subject design made improvements or if a group design failed to find statistical significance. Mixed was reported if some participants improved and others did not or if improvement was reported for some dependent variables, but not for others. Additionally, when possible, the percent of non-overlapping data (PND) was calculated for single-subject designs (Scruggs, Mastropieri, & Casto, 1987), and repeated measures effect sizes were calculated for group designs (Becker, 1988). Repeated measures effect sizes were corrected for bias according to the technique developed by Hedges and Olkin (1985).

The first author extracted information to develop an initial summary of the included studies. The accuracy of these summaries was independently checked by the second author using a checklist that included the initial summary of the study and four questions regarding various details of the study, specifically: (a) is this an accurate summery of the participants? (b) Is this an accurate summary of the restrictive diet? (c) Is this an accurate summary of the results? (d) Is this an accurate summary of the certainty of evidence? The second author read the study and the summary and then completed the checklist. In cases where the summary was not considered accurate, the authors reviewed the study together and summaries were changed to improve accuracy. The resulting summaries were then used in the table.

2.4. Inter-rater agreement

The approach to summarizing studies described above was intended to both ensure the accuracy of the reported summaries, and also to provide a measure of inter-rater agreement (IRA). There were 56 items on which there could be agreement or disagreement (i.e., 15 studies with 4 questions per study). Initial agreement was obtained on 49 items (88%). After discussion agreement was obtained on 100% of items.

The first and second author both independently completed the search procedures and assessed the resulting studies for potential inclusion in the review. The two resulting lists of included studies were then compared to determine agreement for the search and inclusion criteria. Agreement regarding the studies to be included in the review was obtained on 13 out of 14 studies (93%). Initial disagreement occurred concerning the inclusion of Adams and Conn (1997). In that paper, the authors

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present brief case examples of two children before and after implementation of GFCF diets. The dietary changes were implemented by the parents without the direct knowledge of the researchers (exclusion criteria 2). However, once the researchers became aware of the change in diet, they retrospectively evaluated the dietary intervention. Because this retrospective analysis represented an attempt by researchers to systematically analyze the effects of a GFCF diet, it was included in this review.

3. Results

Table 1 summarizes the (a) participants, (b) interventions (c) dependent variables (d) results, and (e) certainty of evidence for each of the 14 included studies. Studies are grouped within the table according to their certainty of evidence classifications. The number of studies within each classification and the results of those studies are summarized above each group.

3.1. Participants

Collectively, the 14 studies provided intervention to a total of 188 participants. The sample size of individual studies ranged from 1 to 50. Most participants (i.e., 126, 67%) were male, 52 (28%) were female, and the gender of the remaining 5% was not reported. Participants were diagnosed with autism (93%) and Asperger syndrome. Participants ranged from 2 to 17 years of age.

3.2. Interventions

The consumption of gluten and/or casein was prohibited in the reviewed studies. One study examined gluten-free diets (Whiteley et al., 1999), a second looked at casein-free diets (Lucarelli et al., 1995), and the remaining 12 evaluated GFCF diets. The length of time the GFCF diet was implemented ranged from 4 days to 4 years (M = 10 months). The studies with negative results implemented the diet for less time (M = 5 weeks, range 4 days to 3 months) than the studies reporting positive results (M = 18 months, range 14 weeks to 4 years). Four studies implemented additional intervention components at the same time the GFCF diet was in effect. These additional components included vitamin supplementation (Adams & Conn, 1997; Patel & Curtis, 2007), elimination of other foods, in addition to gluten or casein (Lucarelli et al., 1995; O'Banion, Armstrong, Cummings, & Stange, 1978; Patel & Curtis, 2007), avoidance of cosmetics/cleaners, administration of citrus abstract, walnut oil, over the counter herbs, injections of vitamin B12, injections of antigens, intravenous chelation, and behavior modification (Patel & Curtis, 2007). One study compared effects of the GFCF diet with behavior modification on challenging behavior in a single-case experimental design (Bird, Russo, & Cataldo, 1977). In that study, the researchers detected no effect on challenging behavior during the implementation of a GFCF diet for 9 days, and then successfully reduced challenging behavior via behavior modification.

3.3. Dependent variables

Dependent variables can be divided into either behavioral or biomedical variables. Behavioral variables measured included communication (e.g., nonverbal communication, vocalizations, question asking), stereotypy, play, and challenging behavior (e.g., pica, self-injury, aggression, and property destruction) (see Table 1). Four studies used only anecdotal reports or researcher created questionnaires to measure behavioral changes (Adams & Conn, 1997; Cade et al., 2000; Patel & Curtis, 2007; Reichelt, Ekrem, & Scott, 1990). The remainder of the studies used direct observation, standardized tests, or a combination of methods to measure changes in the dependent variables. Standardized tests included Diagnose of Psykotisk Adfœrd hos Børn (Diagnosis of Psychotic Behavior in Children, DIPAB) (Haracopos & Kelstrup, 1975), Leiter Nonverbal Intelligence Test (Leiter, 1979), Illinois Test of Psycholinguistic Abilities (ITPA) (Gjessing & Nygaard, 1975), Reynells' Spraktest (Hagtvet & Lillestølen, 1985), Movement Assessment Battery for Children (Henderson & Sugden, 1992), C-Raven Progressive Matrices (C-Raven) (Hansen & Kreiner, 1988), Tajford Observation Scheme (Tajford, 1982), Behavior Summative Evaluation (BSE) (Jacobson & Ackerman, 1990), Kaufmann Assessment Battery for Children (Kaufmann & Kaufmann, 1983), Childhood Autism Rating Scale (CARS) (Schopler, Reichler, DeVellis, & Daly, 1980), and Ecological Communication Orientation Language Sampling Summary (ECO) (MacDonald, Gillette, & Hutchinson, 1989). Biomedical variables measured included the levels of urinary peptides (UPL), relevant enzymes, and antibodies. UPLs were measured using a process called gradient elution high performance liquid chromatography (HPLC (Reichelt & Reichelt, 1997)). Enzymes and antibodies were measured using RIA method (Phadevbas PRIST (Ceska & Lundkvist, 1972)) and the Enzyme Linked Immuno Sorbent Assay (ELISA) (Lucarelli, Zingoni, & Quintieri, 1991).

3.4. Results and certainty of evidence

Seven studies reported positive results (47%) (Adams & Conn, 1997; Cade et al., 2000; Knivsberg, Reichelt, Nodland, & Hoien, 1995; Knivsberg, Wiig, Lind, Nodland, & Reichelt, 1990; Knivsberg et al., 1999, 2002; Patel & Curtis, 2007; Reichelt et al., 1990), four reported negative results (27%) (Bird et al., 1977; Elder et al., 2006; Irvin, 2006; Seung, Rogalski, Shankar, &

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Table 1
Summary of studies restricting ingestion of gluten and/or casein for individuals with autism spectrum disorders.

Citation	Participants	Intervention	Dependent variables	Results and certainty
Studies capable of providing suggestive level of evidence ($n = 11$, 7 with positive results, 2 mixed, 1 negative, and 1 unclear)				
Adams and Conn (1997)	1 male, 1 female 3 years old autism	Two components: (1) Megavitamin (B6 complexes + magnesium + others not stated) (2) GFCF diet for 24 months	Anecdotal parent report of overall behavior	*Results:* Positive; authors report improvements after 2 weeks of intervention, but no quantifiable data is displayed *Certainty:* No experimental design, not enough detail to replicate, no operational definitions, no treatment fidelity, no inter-observer agreement, and no attempt to control alternative explanations
Cade et al. (2000)	28 males, 22 females 3.5–16 years old autism	GFCF diet for 12 months	UPL, blood tests of antibodies to gluten and casein, parent, physician, and teacher ratings of social isolation, eye contact, speech, learning skills, hyperactivity, stereotypical activity, hygiene, panic attacks, and self mutilation	*Results*: Positive; baseline levels of antibodies and UPL were higher in group with autism than in neurotypical control group. Significant changes from baseline on ratings of social isolation, eye contact, speech, learning skills, hyperactivity, stereotypical activity, panic attacks, and self-mutilation *Certainty:* Analysis of antibodies and UPL was conducted at pre-intervention only, no operational definitions of parent and teacher rated behaviors, no treatment fidelity, no inter-observer agreement, no attempt to control alternative explanations, and not blinded
Knivsberg et al. (2002)	10 children *M* age 7.5 years old autism	GFCF diet for 12 months	UPL, Leiter Nonverbal Intelligence Test, linguistic abilities using the ITPA and the Reynells' spraktest, Movement Assessment Battery for Children, parent teacher behavior ratings using the DIPAB	*Results:* Positive; pre–post-test showed improvements DIPAB, and statistically significant changes in the other standardized assessments *Certainty:* Categorizing groups according to gains after intervention increased the likelihood of finding statistical significance, no treatment fidelity, and no attempt to control alternative explanations
Knivsberg et al. (1999)	1 female 7 years old autism	GFCF diet for 24 months	UPL, ITPA, C-Raven, Tafjord Observation Scheme, parent teacher behavior ratings using the DIPAB	*Results:* Positive; authors report improvements in nonverbal communication, stereotypy, and social interactions and claim the girl's behavior was "normalized" *Certainty*: No experimental design, not enough information to replicate, no treatment fidelity, no inter-observer agreement, and no attempt to control alternative explanations
Knivsberg et al. (1990, 1995)[a]	8 males, 7 females 6–14 years old autism	GFCF diet for 48 months	UPL, C-Raven, Tajford Observation Scheme, parent teacher behavior ratings using the DIPAB	*Results:* Positive; improved averages in all dependent variables (language skills after 1 year: RM $\hat{\delta} = 2.07$ and 1.30; language skills after 4 years: RM $\hat{\delta} = 1.27$; social interaction: RM $\hat{\delta} = 2.01$; play-based creativity: RM $\hat{\delta} = 1.32$; motor abilities: RM $\hat{\delta} = 1.43$) and statistically significant decrease in UPL (RM $\hat{\delta} = -0.82$) *Certainty:* No experimental design, not enough information to replicate no treatment fidelity, no inter-observer agreement, and no attempt to control alternative explanations
Lucarelli et al. (1995)	30 males, 6 females 8–13 years old autism	Free of allergens identified for individual participants and restriction of cow's milk for 2 months	BSE, and a battery of Ig antibody tests	*Results:* Mixed; statistically significant reductions in Ig antibody levels, and improvements in 5 of the 7 behaviors measured by the BSE *Certainty:* Results for chemical testing of allergens are conclusive, however, results regarding behavior are suggestive due to no treatment fidelity, no inter-observer agreement, no attempt to control alternative explanations, not blinded, adaptation of BSE
O'Banion et al. (1978)	1 male 8 years old autism	Alternating 4 day periods of fasting (only water allowed) and 4 day periods in which only 1 type of food was allowed per day	Direct observation of challenging behavior, movement, and laughing	*Results:* Unclear; wheat, corn, tomatoes, sugar, mushrooms, and dairy products were suggested by the authors to be associated with increases in behavior *Certainty*: No experimental design, cessation of experiment during key phase of study, extremely high likelihood that carry over effects from extreme food deprivation, stress, and fear confounded data

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Table 1 (*Continued*)

Citation	Participants	Intervention	Dependent variables	Results and certainty
Patel and Curtis (2007)	9 males, 1 female 5–8 years old, 5 with autism + ADHD, and 5 with AS + ADHD	Eight components for 3–6 months: (1) Avoidance of mites, moisture, mold, smoke, pesticides, and toxic cosmetics/cleaners (2) Organic GFCF diet (3) Oral administration of berbine, artemisinin, citrus abstract, and walnut hulls (4) Injections of antigens (5) Administration of common multivitamin and cocktail of over the counter herbs, oils, and extracts, (6) intravenous chelation (7) Injections up to 3 times weekly of vitamin B12 (8) Special education, behavior modification, speech language pathology, occupational therapy, and physical therapy	Urinary metal concentrations and parent report of behavior change	*Results:* Positive; statistically significant decrease in urinary metal concentrations, reported behavioral improvements from parents *Certainty:* No experimental design, no treatment fidelity, no inter-observer agreement and potential behavior improvement from components other than diet (e.g., behavior modification)
Reichelt et al. (1990)	10 males, 5 females 3–17 years old autism	Prescribed participants specific diets based on children's UPL pattern. Diet variations included: GFCF, gluten-restricted, casein-free, and gluten-free, casein-restricted. Each diet was implemented for 12 months.	UPL, blood tests of antibodies, and behavior questionnaire	*Results*: Positive; statistically significant decrease in UPL (IGRM $\hat{\delta} = -1.80$) and improvements in antibodies and behavior *Certainty*: No operational definitions, no treatment fidelity, no inter-observer agreement, and no attempt to control alternative explanations
Seung et al. (2007)	10 males, 3 females 2–16 years old autism	GFCF diet for 3 months	Direct observation of verbal responses to questions, verbal imitations, different words produced, and total utterances	*Results*: Negative; no statistical significance *Certainty*: No control group
Whiteley et al. (1999)	15 males, 3 females *M* age = 5.5 years old, 14 with autism, and 4 with AS	GF diet for 5 months	UPL, parental/teacher interview concerning autistic behaviors, and Kaufmann Assessment Battery for Children	*Results:* Mixed; some statistically significant behavioral improvements, no statistically significant reduction of UPL *Certainty:* No experimental design, no treatment fidelity, no inter-observer agreement, and no attempt to control alternative explanations
Studies capable of providing preponderant level of evidence ($n = 3$, all with negative results)				
Bird et al. (1977)	1 male 9 years old autism	GFCF diet for approximately 9 days	Direct observation of pica, inappropriate vocalizations, cooperation, & motor activity	*Results*: Negative; *PND* = 3% (averaged across dependent variables) *Certainty*: No attempt to control alternative explanations and diet implemented for a brief time
Elder et al. (2006)	12 males, 3 females 2–16 years old ($M = 7.32$) autism	GFCF diet for 6 weeks	UPL, CARS, ECO, and direct observation of initiating communication, responding, and use of intelligible words	*Results:* Negative; no statistical significance *Certainty*: No attempt to control alternative explanations, small and potentially heterogeneous sample, and diet implemented for a brief time
Irvin (2006)	1 male 12 years old autism	GFCF diet for 4 days	Direct observation of self-injury, property destruction, and aggression	*Results:* Negative; *PND* = 0%, and substantial increase in food refusal were noted *Certainty:* No attempt to control alternative explanations and diet implemented for a brief time
Studies capable of providing conclusive level of evidence ($n = 0$)				

Abbreviations: GFCF, gluten-free, casein-free; UPL, urinary peptide level; *M*, mean; DIPAB, Diagnose of Psykotisk Adfærd hos Børn (Diagnosis of Psychotic Behavior in Children); ITPA, Illinois Test of Psycholinguistic Ability; C-Raven, C-Raven Progressive Matrices; RM, repeated measures; BSE, Behavior Summarized Evaluation; ADHD, Attention Deficit Hyperactivity Disorder; AS, Asperger Syndrome; IGRM, Independent Group Repeated Measures; GF, gluten-free; *PND*, Percent Non-overlapping Data; CARS, Childhood Autism Rating Scale; ECO, Ecological Communication Orientation Language Sampling Summary.

[a] Knivsberg et al. (1990) is contained within Knivsberg et al. (1995). The 1990 paper describes the first year of intervention. The 1995 paper describes the maintenance measures taken after 4 years of intervention. Both studies must be read to encounter all the details.

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Elder, 2007), two reported mixed results (13%), (Lucarelli et al., 1995; Whiteley et al., 1999) and in one study the effect of intervention could not be determined (O'Banion et al., 1978).

Quantitative summary of results was possible for 4 studies (Bird et al., 1977; Irvin, 2006; Knivsberg et al., 1990, 1995; Reichelt et al., 1990). Of the 3 single-subject studies reviewed, 2 reported data for which PND values could be calculated (Bird et al., 1977; Irvin, 2006). The PND values were 0% (Irvin, 2006) and 3% (Bird et al., 1977). Of the 9 group-design studies, 2 reported data for which repeated measures effect sizes could be estimated for several dependent variables (Knivsberg et al., 1990, 1995; Reichelt et al., 1990). Data from the other 7 group-design studies, and for the remaining dependent variables from Reichelt et al. (1990) and Knivsberg et al. (1990, 1995) was unfit for use in estimating effect sizes due to missing information (i.e., standard deviations of differences from pre- to post-test), or lack of statistically significant results. When interpreting the following effect sizes, readers should be aware that repeated measures effect sizes are larger than those resulting from independent group, post-test only designs due to the correlation between pre- and post-tests (Dunlap, Cortina, Vaslow, & Burke, 1996; Rosenthal, 1994). In regard to participants' UPLs, the diet treatments were observed to have effect sizes of −1.80 (Reichelt et al., 1990), and −0.82 (Knivsberg et al., 1990, 1995). For language skills-related variables, Knivsberg et al. (1995) observed effect sizes of 2.07 and 1.30 after 1 year of treatment, as measured with the ITPA and Tajford, respectively, and 1.27 after 4 years of treatment, as measured with the ITPA. Using the C-Raven to measure nonverbal problem solving, Knivsberg et al. (1990, 1995) observed effect sizes of 2.47 and 2.71, after 1 and 4 years, respectively. Knivsberg et al. (1990) also observed effect sizes of 2.01 for social interaction, 1.32 for play-based creativity, and 1.43 for motor abilities, as measured by the Tajford after 1 year of treatment. Confidence intervals for the effect size estimates were not calculated, and statistical tests of significance were not performed due to the inadequate size of study samples and the resulting instability of variance estimates (Hedges & Olkin, 1985).

All of the studies reporting positive results were classified at the lowest level of certainty (suggestive). All studies at the second level (preponderant) reported negative results. None of the reviewed studies were capable of providing conclusive evidence. Of the 14 studies, 6 (43%) did not utilize an experimental design (Adams & Conn, 1997; Knivsberg et al., 1990, 1995, 1999; O'Banion et al., 1978; Patel & Curtis, 2007; Whiteley et al., 1999), 3 (21%) did not provide enough detail to enable replication of the procedures (Adams & Conn, 1997; Knivsberg et al., 1990, 1995, 1999), 3 (21%) did not operationally define the dependent variables (Adams & Conn, 1997; Cade et al., 2000; Reichelt et al., 1990), 9 (64%) did not measure treatment fidelity (Adams & Conn, 1997; Cade et al., 2000; Knivsberg et al., 1990, 1995, 1999, 2002; Lucarelli et al., 1995; Patel & Curtis, 2007; Reichelt et al., 1990; Whiteley et al., 1999), 8 (57%) did not measure inter-observer agreement (Adams & Conn, 1997; Cade et al., 2000; Knivsberg et al., 1990, 1995, 1999; Lucarelli et al., 1995; Patel & Curtis, 2007; Reichelt et al., 1990; Whiteley et al., 1999), 13 (93%) did not attempt to control other potential explanations of behavior change (Adams & Conn, 1997; Bird et al., 1977; Cade et al., 2000; Elder et al., 2006; Irvin, 2006; Knivsberg et al., 1990, 1995, 1999, 2002; Lucarelli et al., 1995; O'Banion et al., 1978; Patel & Curtis, 2007; Reichelt et al., 1990; Whiteley et al., 1999), 3 (21%) did not use a blinding procedure when it would have been appropriate (Cade et al., 2000; Lucarelli et al., 1995; Reichelt et al., 1990), and 4 (29%) implemented other interventions at the same time as the GFCF diet (Adams & Conn, 1997; Lucarelli et al., 1995; O'Banion et al., 1978; Patel & Curtis, 2007). Twelve (86%) of the studies contained more than one of the above listed methodological limitations (Adams & Conn, 1997; Cade et al., 2000; Elder et al., 2006; Irvin, 2006; Knivsberg et al., 1990, 1995, 1999, 2002; Lucarelli et al., 1995; O'Banion et al., 1978; Patel & Curtis, 2007; Reichelt et al., 1990; Whiteley et al., 1999).

4. Discussion

Our systematic search yielded 14 studies involving the treatment of ASD by restricting the intake of gluten and/or casein. Summaries of these studies revealed that the existing literature base is best described as very limited with respect to the overall scope and quality of the research. In terms of scope, the current database must be considered limited because of the sheer paucity of studies. In terms of methodological quality, the current database contains no studies that are capable of providing conclusive evidence, and only eight studies that utilized a recognizable experimental design. Of these eight, only three studies were of sufficient experimental rigor to qualify at the preponderant level of certainty.

Based on this review, we must conclude that the published studies we located do not support the use of GFCF diets in the treatment of ASD. Additionally, the data from these studies do not support the Opioid-Excess Theory. Until conclusive evidence is found in support of GFCF diets, restrictive diets should only be implemented in the event a food allergy or intolerance is detected (Berni, Ruotolo, Discepolo, & Troncone, 2008; Zopf, Baenkler, Silbermann, Hahn, & Raithel, 2009). Below, the lack of support is discussed with respect to problems regarding internal, measurement, and construct validity, and plausible alternative explanations for study outcomes.

4.1. Problems with internal validity

All studies that reported positive results, and one study that reported mixed results, did not implement controls for maturation effects (Adams & Conn, 1997; Cade et al., 2000; Knivsberg et al., 1990, 1995, 1999, 2002; Lucarelli et al., 1995; Patel & Curtis, 2007; Reichelt et al., 1990; Whiteley et al., 1999). The studies employed post-treatment measures only (Adams & Conn, 1997; Patel & Curtis, 2007; Reichelt et al., 1990), an AB design (Knivsberg et al., 1999), or did not include a control group (Cade et al., 2000; Knivsberg et al., 1990, 1995; Lucarelli et al., 1995; Patel & Curtis, 2007; Reichelt et al., 1990;

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Whiteley et al., 1999). In these cases, natural development processes, and individuals' learning from events separate from the treatment, could account for some to all of the positive change within participants on dependent measures.

4.2. Problems with measurement validity

All studies reporting positive effects used measures and/or measurement conditions subject to bias (Adams & Conn, 1997; Cade et al., 2000; Knivsberg et al., 1990, 1995, 1999, 2002; Patel & Curtis, 2007; Reichelt et al., 1990; Whiteley et al., 1999). The measures (a) recorded subjective perceptions of teachers, parents, and physicians who were not blind to treatment conditions, (b) often required the teachers, parents, and physicians to make judgments based on their memories from long spans of time (Adams & Conn, 1997; Knivsberg et al., 1990, 1999; Patel & Curtis, 2007; Reichelt et al., 1990; Whiteley et al., 1999), and/or (c) contained researcher developed surveys (Adams & Conn, 1997; Knivsberg et al., 1990; Patel & Curtis, 2007; Reichelt et al., 1990; Whiteley et al., 1999).

The absence of blindness to treatment conditions could have allowed placebo effects to influence measurement outcomes. Teachers', parents', and physicians' beliefs and personal investments in positive study results may have influenced perceptions and biased their post-treatment input regarding dependent variables. Additionally, the lack of blinding could have created scenarios in which parents and teachers, intensely hoping for a profound treatment effect, may have inadvertently influenced dependent variables. For example, a parent who believes the diet is working to improve challenging behavior may in fact begin noticing positive behaviors that were present prior to diet implementation. If such an increase in awareness leads to an increase in parental praise for the appropriate behavior, and subsequently increases in the appropriate behavior, then behavioral improvements unrelated to the removal of gluten and casein may be detected by dependent measures. This potential source of bias was specifically mentioned by Elder et al. (2006).

Reliance on the memories of teachers, parents, and physicians could have also biased post-treatment outcomes. In a similar manner as mentioned above, placebo effects that impact perception, and humans' tendency to reframe past events to match present conceptions could have allowed measures to register positive gains, or large improvements, when in fact there were none, or they were of trivial magnitude (Conway & Ross, 1984; Levine, 1997). Researcher developed measures are problematic due to their association with larger effect sizes than those typically found with comparable standardized measures (Kim, Vaughn, Wanzek, & Wei, 2004). For researcher developed surveys, the problem is two-fold, as research has found survey question characteristics, such as wording, can bias responses (Schwarz, 2008).

4.3. Problems with construct validity

Across studies that refute or do not provide evidence for the efficacy of the GFCF diet, short diet durations pose problems of construct validity (Bird et al., 1977; Elder et al., 2006; Irvin, 2006; O'Banion et al., 1978; Seung et al., 2007). For the group of four such studies, diet durations ranged from 4 days to 12 weeks. Due to time issues related to the Opioid-Excess Theory, valid testing of possible effects of the GFCF diet may require implementation periods of longer than 12 weeks. Residue of gluten and its byproducts are known to remain in the intestines of patients with Celiac Disease for up to 12 weeks after ceasing gluten consumption (Kumar, O'Donoghue, Stenson, & Dawson, 1979). The similarity between the mechanisms of action involved in Celiac Disease, and that proposed by the Opioid-Excess Theory, warrants speculation that residue of gluten and its byproducts may also remain in atypically functioning intestines of children with autism. As long as residues remain in a child's intestines, it is possible that the effect of a GFCF diet would remain latent. Therefore, proper testing of the Opioid-Excess Theory may require extending the diet beyond 12 weeks.

4.4. An additional plausible alternative explanation for study outcomes

If a child with ASD is hypersensitive to gluten or dairy, due to a normally occurring allergy or intolerance, then their ingestion may simply cause an upset stomach. A competing explanation for the observed effects of the GFCF diet is that an upset stomach may act as a motivating operation affecting socially mediated consequences (Carr, Smith, Giacin, Whelan, & Pancari, 2003; O'Reilly, 1995; O'Reilly, Lacey, & Lancioni, 2000). For example, a child with an upset stomach may find the demands of completing school work more aversive than they would without such an illness. Subsequently, they may engage in increased levels of challenging behavior with the intent of escaping those demands.

Biological motivating operations have been demonstrated to effect behaviors often associated with developmental disabilities. Carr et al. (2003) demonstrated that menstrual discomfort in three women with intellectual disabilities led to an increase in aggression, self-injury, and tantrums when they were asked to complete work. O'Reilly (1995) demonstrated that a lack of sleep contributed to the levels of aggression in a 31-year-old man with severe intellectual disabilities when he was presented with task demands. O'Reilly et al. (2000) examined the influence of background noise on levels of problem behavior and pain behavior for a child with Williams syndrome and hyperacusis. Background noise was associated with increases in escape-maintained problem behavior and increases in pain behavior (e.g., crying). In each of these examples, a biological variable causing pain or discomfort (i.e., menstruation, sleep deprivation, and ear ache) led to increases in behaviors commonly associated with developmental disabilities under certain social contexts (i.e., receiving a request to do work). The notion that an upset stomach caused by a food allergy might act in a similar way for children with ASD who are

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allergic to certain foods may account for positive study outcomes with greater parsimony than the Opioid-Excess Theory, in which food-related illness is believed to actually cause ASD.

Unfortunately, just two studies that restricted diets for individuals with ASD involved identification of food allergies. Lucarelli et al. (1995) assessed participants' food allergies and excluded identified allergens as part of a restricted diet. The researchers did not correlate, or otherwise examine relationships between food allergies, levels of baseline behaviors, and post-dieting behaviors. Bird et al. (1977) implemented a gluten-free diet for a participant with a known wheat allergy. The durations of diet phases in their ABA design were 11 and 8 days. Due to the brevity of diet phases and the resulting lack of construct validity, the study was unable to comment on the existence of a functional relation between the diet and the behavior of a person with a wheat allergy.

4.5. Summary and implications for practice

Based on the results of this review, it would appear that evidence in support of Opioid-Excess Theory and the resulting treatment of ASD with the GFCF diet is limited and weak. Adverse consequences potentially associated with GFCF diets (e.g., stigmatization, diversion of treatment resources, reduced bone cortical thickness) further the argument against the diet's therapeutic use. Controversy and conflicting research findings concerning the Opioid-Excess Theory renders other explanations for observed benefits plausible (e.g., biological motivating operations influence behavior). Should a child with ASD experience acute behavioral changes, seemingly associated with changes in diet, practitioners should consider testing the child for allergies and food intolerances, and subsequently eliminate identified allergens and irritants from their environment. Should future research support the therapeutic use of GFCF diets, over and above benefits derived from allergen and irritant avoidance, it would seem reasonable to undertake a controlled trial to determine if a GFCF diet had any additional therapeutic benefit for individual children with ASD.

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